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## Hotspots in Neuro-Oncology

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# Hotspots in Neuro-Oncology

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## ■ Rituximab Is Associated with Improved Survival for Aggressive B cell CNS Lymphoma

*Gregory G, et al. Neuro-Oncology 2013; 15: 1068–73.*

Despite the absence of evidence for its activity, the CD20 antibody rituximab has been broadly introduced into the primary treatment of primary central nervous system lymphoma (PCNSL). In the August issue, Gregory et al from Australia sought to validate this approach by a retrospective study of 128 patients with PCNSL treated with or without rituximab. On univariate analysis, younger age, ECOG performance status 0 or 1, normal lactate dehydrogenase, diagnosis after 2004, and treatment with cytarabine and rituximab were predictive of favourable overall survival. On multivariate analysis, only age was an independent predictor of survival. The interpretation of these results is difficult. Given that treatment outcome is likely to improve due to many reasons over time and that multivariate analysis failed to show a role either for rituximab or for treatment after 2004, I doubt that this data can be used to justify the routine introduction of rituximab into standards of care for PCNSL. Prospective randomised trials are the only way to move this complex field forward.

## ■ Subsequent Brain Tumors in Patients with Autoimmune Disease

*Hemminki K, et al. Neuro-Oncology 2013; 15: 1142–50.*

Interrelations between various autoimmune diseases and the incidence and cause of various brain tumours have remained a controversial topic in the epidemiology of brain tumours. No firm conclusions have been derived from previous studies. For the present study, data were derived from Sweden. Data on 402,462 patients hospitalised for autoimmune diseases were studied, brain tumour risks and survival were analyzed and compared with that of the general population. Among 33 autoimmune diseases, none had an impact on the incidence of brain tumours; however, there was a negative impact on survival both in gliomas and in meningiomas. The reasons for this remain unclear but may include enhanced physical disability or under-treatment because of limitations of cancer treatment by the pre-existing autoimmune disorder. Thus, while there have been claims that gliomas may even be underrepresented in patients with allergies because of enhanced immune reactivity, no link between the evolution of brain tumours and autoimmune dysfunction was disclosed here.

## ■ Memantine for the Prevention of Cognitive Dysfunction in Patients Receiving Whole-Brain Radiotherapy: A Randomized, Double-Blind, Placebo-Controlled Trial

*Brown PD, et al. Neuro-Oncology 2013; 15: 1429–37.*

Whole-brain radiotherapy has been increasingly challenged in the treatment of various neuro-oncological conditions because of insufficient efficacy and its unfavourable, notably long-term safety profile. Efforts at improving or maintaining cognitive function in irradiated patients have so far not been successful. In the October issue, Brown et al, for the Radiation Therapy Oncology Group (RTOG), presented results of a randomised controlled trial which assessed the possible benefit of the candidate neuroprotective agent, memantine, in brain metastasis patients treated with whole-brain radiotherapy. Although the mode of action of memantine in other neurological conditions has not been fully clarified, antagonism at the N-methyl-D-aspartate type of the glutamate receptor is currently thought to mediate these effects. Although the trial failed to meet the primary endpoint, in part as a result of insufficient power, secondary endpoints and subgroup analysis indicated that memantine-treated patients had superior cognitive function over time. These interesting results provide support for further exploration of similar pharmacological approaches in patients with brain metastases for whom whole-brain radiotherapy seems to be indicated and indispensable. Various candidate drugs are in principle available and similar trials are eagerly awaited.

## ■ The Immune Cell Infiltrate Populating Meningiomas is Composed of Mature, Antigen-Experienced T and B Cells

*Fang L, et al. Neuro-Oncology 2013; 15: 1479–90.*

Meningioma is not commonly a tumour considered to trigger a significant immune response. Moreover, it has not been a target disease for the increasing number of immunotherapy approaches currently applied to other brain tumours, notably glioblastoma. In the November issue, Fang et al assess the immune cell infiltrate of a series of 28 meningiomas and observed significant numbers of B and T cells, in particular around vessels. In most tumours, flow cytometry of ex vivo harvested tumour tissue was used to further characterise T cell phenotypes. The tumours commonly contained antigen-ex-

perienced CD4+ and CD8+ memory/effector T cells, regulatory T cells, and T cells expressing PD-1 und Tim-3. These T cell populations were enriched compared with peripheral blood. These studies highlight that there are specific interactions even between meningiomas and the immune system and illustrate the possibility for future immunological approaches particularly in tumours where surgical and radio-oncological treatment strategies have failed.

### ■ Seizure Control Following Radiotherapy in Patients with Diffuse Gliomas: A Retrospective Study

*Rudà R, et al. Neuro-Oncology 2013; 15: 1739–49.*

Symptomatic epilepsy is a common presenting sign and associated with significant impairment of quality of life in patients with low-grade gliomas. Since imaging endpoints have remained controversial in these patients, measures of clinical

benefit would be helpful in defining a role for any treatment in patients with low-grade gliomas. In the December issue, Rudà et al reported on the effect on seizure control of radiotherapy in patients with diffuse gliomas. In a retrospective study of 43 patients with low-grade gliomas, there was a significant reduction of seizure frequency in 31 of 43 patients (73 %) at 3 months after radiotherapy. Seizure freedom was achieved in 32 % of all patients at 12 months. Effects on seizures were not necessarily reflected by effects visible on MR imaging. These interesting study results suggest that the impact of therapeutic measures for low-grade gliomas on seizure frequency should be incorporated as an endpoint in future clinical trials.

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**Gregory G, Arumugaswamy A, Leung T, Chan KL, Abikhair M, Tam C, Bajel A, Cher L, Grigg A, Ritchie D, Opat S. Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. Neuro-Oncology 2013;15:1068-1073**

Despite the absence of evidence for its activity, the CD20 antibody rituximab has been broadly introduced into the primary treatment of primary central nervous system lymphoma (PCNSL). In the August issue, Gregory and colleagues from Australia sought to validate this approach by a retrospective study of 128 patients with PCNSL treated with or without rituximab. On univariate analysis, younger age, ECOG performance status 0 or 1, normal lactate dehydrogenase, diagnosis after 2004 and treatment with cytarabine and rituximab were predictive of favourable overall survival. On multivariate analysis only age was an independent predictor of survival. The interpretation of these results is difficult. Given that treatment outcome is likely to improve due to many reasons over time and that the multivariate analysis failed to show a role either for rituximab or for treatment after 2004, I doubt that this data can be used to justify the routine introduction of rituximab into standards of care for PCNSL. Prospective randomized trials are the only way to move this complex field forward.

**Hemminki K, Liu X, Försti A, Ji J, Sundquist J, Sundquist K. Subsequent brain tumors in patients with autoimmune disease. Neuro-Oncology 2013;15:1142-1150**

Interrelations between various autoimmune diseases and the incidence and cause of various brain tumors have remained a controversial topic in the epidemiology of brain tumors. No firm conclusions have been derived from previous studies. For the present study, data were derived from Sweden. Data on 402,462 patients hospitalized for autoimmune diseases were studied, brain tumor risks and survival were analyzed and compared with that of the general population. Among 33 autoimmune diseases, none had an impact on the incidence of brain tumors, however, there was a negative impact on survival both in gliomas and in meningiomas. The reasons for this remain unclear but may include enhanced physical disability or under-treatment because of limitations of cancer treatment by the preexisting autoimmune disorder. Thus, while there have been claims that gliomas may even be underrepresented in patients with allergies because of enhanced immune reactivity, no link between the evolution of brain tumors and autoimmune dysfunction was disclosed here.

**Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, Choucair A, Fox S, Suh JH, Roberge D, Kavadi V, Bentzen SM, Mehta MP, Watkins-Bruner D, for the Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncology 2013;15:1429-1437**

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**Fang L, Lowther DE, Meizlish ML, Anderson RCE, Bruce JN, Devine L, Huttner AJ, Kleinstein SH, Lee JY, Stern JNH, Yaari G, Lovato L, Cronk KM, O'Connor KC. The immune cell infiltrate populating meningiomas is composed of mature, antigen-experienced T and B cells. *Neuro-Oncology* 2013;15:1479-1490**

Meningioma is not commonly a tumor considered to trigger a significant immune response. Moreover, it has not been a target disease for the increasing number of immunotherapy approaches currently applied to other brain tumors, notably glioblastoma. In the November issue, Fang and colleagues assess the immune cell infiltrate of a series of 28 meningiomas and observed significant numbers of B and T cells, in particular around vessels. In most tumors flow cytometry of ex vivo harvested tumor tissue was used to further characterize T cell phenotypes. The tumors commonly contained antigen-experienced CD4+ and CD8+ memory/effector T cells, regulatory T cells, and T cells expressing PD-1 and Tim-3. These T cell populations were enriched compared with peripheral blood. These studies highlight that there are specific interactions even between meningiomas and the immune system and illustrate the possibility for future immunological approaches particularly in tumors where surgical and radiooncological treatment strategies have failed.

**Rudà R, Magliola U, Bertero L, Trevisan E, Bosa C, Mantovani C, Ricardi U, Castiglione A, Monagheddu C, Soffietti R. Seizure control following radiotherapy in patients with diffuse gliomas: a retrospective study. *Neuro-Oncology* 2013;15:1739-1749**

Symptomatic epilepsy is a common presenting sign and associated with significant impairment of quality of life in patients with low-grade gliomas. Since imaging endpoints have remained controversial in these patients, measures of clinical benefit would be helpful in defining a role for any treatment in patients with low grade gliomas. In the December issue, Rudà and colleagues reported on the effect on seizure control of radiotherapy in patients with diffuse gliomas. In a retrospective study of 43 patients with low-grade gliomas, there was a significant reduction of seizure frequency in 31 of 43 patients (73%) at 3 months after radiotherapy. Seizure freedom was achieved in 32% of all patients at 12 months. Effects on seizures were not necessarily reflected by effects visible on MR imaging. These interesting study

results suggest that the impact of therapeutic measures for low-grade gliomas on seizure frequency should be incorporated as an endpoint in the future in clinical trials.